



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

46037 7590 08/19/2010

OTT-NIH
C/O EDWARDS ANGELL PALMER & DODGE LLP
PO BOX 55874
BOSTON, MA 02205

EXAMINER

MARVICH, MARIA

ART UNIT

PAPER NUMBER

1633

DATE MAILED: 08/19/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/566,886

02/01/2006

David M. Neville

84120(47992)

9182

TITLE OF INVENTION: METHODS FOR EXPRESSION AND PURIFICATION OF IMMUNOTOXINS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1510	\$300	\$0	\$1810	11/19/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

46037 7590 08/19/2010

OTT-NIH
C/O EDWARDS ANGELL PALMER & DODGE LLP
PO BOX 55874
BOSTON, MA 02205

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/566,886	02/01/2006	David M. Neville	84120(47992)	9182
------------	------------	------------------	--------------	------

TITLE OF INVENTION: METHODS FOR EXPRESSION AND PURIFICATION OF IMMUNOTOXINS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
-------------	--------------	---------------	---------------------	----------------------	------------------	----------

nonprovisional	NO	\$1510	\$300	\$0	\$1810	11/19/2010
----------------	----	--------	-------	-----	--------	------------

EXAMINER	ART UNIT	CLASS-SUBCLASS
----------	----------	----------------

MARVICH, MARIA	1633	435-069100
----------------	------	------------

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s); (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,886	02/01/2006	David M. Neville	84120(47992)	9182
46037	7590	08/19/2010	EXAMINER	
			MARVICH, MARIA	
			ART UNIT	PAPER NUMBER
			1633	
DATE MAILED: 08/19/2010				

OTT-NIH
C/O EDWARDS ANGELL PALMER & DODGE LLP
PO BOX 55874
BOSTON, MA 02205

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability

Application No.

10/566,886

Applicant(s)

NEVILLE ET AL.

Examiner

MARIA B. MARVICH

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 2/25/10.
2. ☒ The allowed claim(s) is/are 1-26 and 39-49.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
- * Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date ____.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|---|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input type="checkbox"/> Notice of Informal Patent Application |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6. <input type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date ____. |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date ____ | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 8. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9. <input type="checkbox"/> Other ____. |

DETAILED ACTION

This office action is in response to an amendment filed 8/9/10. Claims 1-26 and 39-49 are pending in the application.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Colleen J. McKiernan on 8/9/10.

The application has been amended as follows:

IN THE CLAIMS:

Claim 1. (Currently amended) A method of expressing an immunotoxin in a *Pichia pastoris* that expresses the immunotoxin, the method comprising:

- a) growing the *Pichia pastoris* in a growth medium comprising an enzymatic digest of protein and yeast extract ~~that expresses~~ wherein the immunotoxin coding sequence is under control of an AOX1 promoter ~~in a growth medium comprising an enzymatic digest of protein and yeast extract;~~ and

Art Unit: 1633

b) performing methanol induction on the cultured *Pichia pastoris*, wherein the methanol induction is performed at a temperature ~~[[of]]~~ comprising 17.5°C ~~[[and]]~~ or below.

Claim 2. (currently amended) The method of claim 1, wherein the methanol induction comprises a limited methanol feed comprising administration of methanol at a concentration of between 0.5-0.75 ml/min (per 10 L initial growth medium).

Claim 3. (currently amended) The method of claim 1, wherein the methanol induction comprises administration of a methanol and glycerol containing feed.

Claim 14. (Currently amended) The method of claim 12, wherein the phenylmethanesulfonyl fluoride is dissolved in a 4:1 methanol: glycerol induction feed and the concentration of phenylmethanesulfonyl fluoride does not exceed 10 mM.

Claim 25. (Currently amended) A method of expressing an immunotoxin in a *Pichia pastoris* that expresses the immunotoxin, the method comprising:

- a) growing the *Pichia pastoris* in a growth medium comprising an enzymatic digest of protein and yeast extract ~~that expresses~~ wherein the immunotoxin coding sequence is under control of an AOX1 promoter ~~in a growth medium comprising an enzymatic digest of protein and yeast extract~~; and
- b) performing methanol induction on the *Pichia pastoris*, wherein the methanol

Art Unit: 1633

induction comprises a limited methanol feed comprising administration of methanol at a concentration of 0.5-0.75 ml/min/10L of initial volume of the growth medium, wherein the induction is performed at a temperature comprising 17.5°C -~~[[and]]~~ or below, ~~wherein~~ further comprising an antifoaming agent ~~supplied~~ in the growth medium at a concentration of up to 0.07%, wherein agitation is maintained at about 400 RPM during the induction step, and wherein the induction step is performed for between about 22 and 288 h.

26. (Currently amended) A method of expressing an immunotoxin in a *Pichia pastoris* that expresses the immunotoxin, the method comprising:

- a) growing the *Pichia pastoris* in a growth medium comprising about 4% glycerol, about 2% yeast extract, about 2% enzymatic digest of soy protein, about 1.34% yeast nitrogen base with ammonium sulfate and without amino acids, and about 0.43% PTM1 solution ~~that expresses wherein the immunotoxin coding sequence is under control of an AOX1 promoter in a growth medium comprising about 4% glycerol, about 2% yeast extract, about 2% enzymatic digest of soy protein, about 1.34% yeast nitrogen base with ammonium sulfate and without amino acids, and about 0.43% PTM1 solution~~, wherein the growth occurs at a pH of about 3.5, and wherein the dissolved oxygen concentration in the growth medium is maintained at a value of 40% or higher; and
- b) performing methanol induction on the *Pichia pastoris*, wherein the methanol induction comprises a limited methanol feed comprising administration of methanol at a concentration of 0.5-0.75 ml/min/10L of initial volume of growth

Art Unit: 1633

medium, wherein the induction is performed at a temperature ~~[[is]]~~ of 15°C, wherein the pH of the growth medium during the induction step is about 7.0, ~~wherein~~ further comprising an antifoaming agent ~~supplied~~ at a concentration of 0.02%, wherein the agitation is maintained at about 400 RPM during the induction step, and wherein the induction step is performed for about 163 h.

41. (Currently Amended) The method of claim 1, wherein the induction is performed for at least 4 hours and the temperature is ramped down from 28°C during the growth phase to 15°C during the first four hours of methanol induction.

42. (Currently Amended) The method of claim 25, wherein the induction is performed for at least 4 hours and the temperature is ramped down from 28°C during the growth phase to 15°C during the first four hours of methanol induction.

In claim 44, line 2, delete the word “and” prior to “below for at least” and replace it with the word --or--.

In claim 45, line 2, delete the word “and” prior to “below for at least” and replace it with the word --or--.

In claim 46, line 2, delete the word “and” prior to “below for at least” and replace it with the word --or--.

Art Unit: 1633

In claim 47, line 2, delete the word “and” prior to “below for at least” and replace it with the word --or--.

In claim 48, line 2, delete the word “and” prior to “below for at least” and replace it with the word --or--.

In claim 49, line 2, delete the word “and” prior to “below for at least” and replace it with the word --or--.

Conclusion

The claims have been renumbered in the following order: Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 39, 40, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 41, 44, 45, 25, 42, 46, 47, 26, 43, 48, and 49.

Claims 1, 25 and 26 have been amended to place limitations in proper proximity with the characteristics they modify. Secondly, it is more accurate to recite that the coding sequence is linked to the promoter as opposed to the immunotoxin in each of these claims. Finally, in claims 1-3, 14, 25 and 26 claim language was amended to refer in completeness to the methanol concentrations therein as well as inclusion of antifoaming agents. Claims 41 and 42 were incomplete as recited. However, a search of the specification only found a single reference to ramping of temperature and that was from 28°C during the growth phase to 25°C -15°C during the methanol induction phase. This means that the claim language in the base claims of the induction temperature with

Art Unit: 1633

an upper range of 17.5°C cannot be if as in claims 41 and 42, the induction occurs from 28-25-15. This range is outside of that for claims 1 and 25.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
Primary Examiner, Art Unit 1633